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(54) **Title:** TETRAHYDROINDOLONE DERIVATIVES AS GABAAALPHA5 LIGANDS FOR ENHANCING COGNITION

(57) Abstract

The present invention provides compounds of formula (I) where A is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl C_{1-6} alkyl, or aryl wherein the aryl group is optionally substituted by halogen, C_{1-6} alkyl, CF_3, CN, NO_2 or NH_2, NR^1R^{10}, $S(O)_pR^1$, heteroaryl C_{1-6} alkyl or heteroaryl; B is phenyl or a 5–membered ring, a 6–membered heteroaromatic ring substituted by one or more substituents independently chosen from: cyano; and aryl, aryl C_{1-6} alkyl or a 5–membered ring; R^2 and R^3 are independently hydrogen or C_{1-6} alkyl or together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group; pharmaceutical compositions comprising them; their use in therapy and in the manufacture of medicaments for enhancing cognition, for example in Alzheimer's Disease, particularly through acting at the $GABA_A$ $\alpha 5$ receptor subunit; and methods of treatment using them.

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TETRAHYDROINDOLONE DERIVATIVES AS GABAAALPHA5 LIGANDS FOR ENHANCING COGNITION

The present invention relates to tetrahydroindolone derivatives, pharmaceutical compositions comprising them and to their use in therapy. More particularly, this invention is concerned with substituted derivatives which are ligands for $GABA_A$ receptors, in particular for $GABA_A$ $\alpha5$ receptors and are therefore useful in therapy particularly where cognition enhancement is required.

Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) $GABA_A$ receptors, which are members of the ligand-gated ion channel superfamily; and (2) $GABA_B$ receptors, which may be members of the G-protein linked receptor superfamily. Since the first cDNAs encoding individual $GABA_A$ receptor subunits were cloned the number of known members of the mammalian family has grown to thirteen (six α subunits, three β subunits, three γ subunits and one δ subunit). It may be that further subunits remain to be discovered; however, none has been reported since 1993.

Although knowledge of the diversity of the $GABA_A$ receptor gene family represents a huge step forward in our understanding of this ligand-gated ion channel, insight into the extent of subtype diversity is still at an early stage. It has been indicated that an α subunit, a β subunit and a γ subunit constitute the minimum requirement for forming a fully functional $GABA_A$ receptor expressed by transiently transfecting cDNAs into cells. As indicated above, a δ subunit also exists, but is apparently uncommon in the native receptor.

Studies of receptor size and visualisation by electron microscopy conclude that, like other members of the ligand-gated ion channel family, the native $GABA_A$ receptor exists in pentameric form. The selection of at least one α, one β and one γ subunit from a repertoire of thirteen allows for the possible existence of more than 10,000 pentameric subunit combinations. Moreover, this calculation overlooks the additional

permutations that would be possible if the arrangement of subunits around the ion channel had no constraints (i.e. there could be 120 possible variants for a receptor composed of five different subunits).

Receptor subtype assemblies which do exist include $\alpha1\beta2\gamma2$, $\alpha2\beta2/3\gamma2$, $\alpha3\beta\gamma2/3$, $\alpha2\beta\gamma1$, $\alpha5\beta3\gamma2/3$, $\alpha6\beta\gamma2$, $\alpha6\beta\delta$ and $\alpha4\beta\delta$. Subtype assemblies containing an $\alpha1$ subunit are present in most areas of the brain and account for over 40% of $GABA_A$ receptors in the rat. Subtype assemblies containing $\alpha2$ and $\alpha3$ subunits respectively account for about 25% and 17% of $GABA_A$ receptors in the rat. Subtype assemblies containing an $\alpha5$ subunit are primarily hippocampal and represent about 4% of receptors in the rat.

A characteristic property of some $GABA_A$ receptors is the presence of a number of modulatory sites, of which the most explored is the benzodiazepine (BZ) binding site through which anxiolytic drugs such as diazepam and temazepam exert their effect. Before the cloning of the $GABA_A$ receptor gene family, the benzodiazepine binding site was historically subdivided into two subtypes, BZ1 and BZ2, on the basis of radioligand binding studies. The BZ1 subtype has been shown to be pharmacologically equivalent to a $GABA_A$ receptor comprising the $\alpha1$ subunit in combination with $\beta2$ and $\gamma2$. This is the most abundant $GABA_A$ receptor subtype, representing almost half of all $GABA_A$ receptors in the brain.

Two other major populations are the $\alpha2\beta\gamma2$ and $\alpha3\beta\gamma2/3$ subtypes. Together these constitute approximately a further 35% of the total $GABA_A$ receptor repertoire. Pharmacologically this combination appears to be equivalent to the BZ2 subtype as defined previously by radioligand binding, although the BZ2 subtype may also include certain $\alpha5$-containing subtype assemblies. The physiological role of these subtypes has hitherto been unclear because no sufficiently selective agonists or antagonists were known.

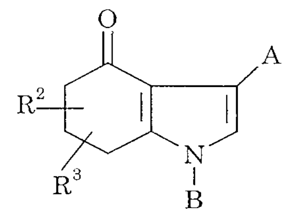
It is now believed that agents acting as BZ agonists at $\alpha1\beta\gamma2$, $\alpha2\beta\gamma2$ or $\alpha3\beta\gamma2$ subunits will possess desirable anxiolytic properties. The $\alpha1$-selective $GABA_A$ receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through $GABA_A$ receptors containing the $\alpha1$ subunit. Accordingly, it is considered that $GABA_A$ receptor agonists which bind more effectively to the $\alpha2$ and/or $\alpha3$ subunit than to $\alpha1$ will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Also, agents which are antagonists or inverse agonists at $\alpha1$ might be employed to reverse sedation or hypnosis caused by $\alpha1$ agonists.

A number of dementing illnesses such as Alzheimer's disease are characterised by a progressive deterioration in cognition in the sufferer. It would clearly be desirable to enhance cognition in subjects desirous of such treatment, for example for subjects suffering from a dementing illness. It is believed this can be done utilising compounds which are ligands for the $GABA_A$ $\alpha5$ receptor subtype.

WO-A-9616954 mentions three thienylcyclohexanone derivatives substituted by substituted arylaminocarbonyl on the thiophene ring as fungicides.

Van Rhee *et al*, *J. Med. Chem.*, 1996, **39**, 398-406 discloses related compounds as adenosine receptor antagonists which differ in having an ester group on the thiophene ring.

The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

where A is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, arylC_{1-6}alkyl, or aryl wherein the aryl group is optionally substituted by halogen, C_{1-6} alkyl, CF_3, CN, NO_2 or NH_2, NR^1R^{10}, $S(O)_pR^1$, heteroarylC_{1-6}alkyl or heteroaryl where heteroaryl is a 5- or 6-membered heteroaromatic ring as defined for B below;

B is phenyl or a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, a 6-membered heteroaromatic ring containing 1, 2, 3 or 4 nitrogen atoms, each of which rings is optionally substituted by one or more substituents independently chosen from: cyano; C_{1-6}alkyl; C_{1-6}haloalkyl; halogen; $S(O)_rR^4$; COR^5; and aryl, arylC_{1-6}alkyl or a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N wherein the aryl ring or 5-membered ring is optionally substituted by one, two or three substituents independently chosen from halogen, CF_3, OCH_3, nitro and cyano; and when a nitrogen ring atom is present it is optionally substituted by oxygen;

R^1 is hydrogen; C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl or C_{3-6}cycloalkenyl each of which is optionally substituted by amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, C_{1-6}alkoxy, C_{1-6}alkylaminocarbonyl, one, two or three hydroxy groups, one, two or three halogen atoms or a four, five or six-membered saturated heterocyclic ring containing a nitrogen atom and optionally either an oxygen atom or a further nitrogen atom which ring is optionally substituted by C_{1-4}alkyl on the further

nitrogen atom; aryl, arylC_{1-6}alkyl, arylC_{2-6}alkenyl or arylC_{2-6}alkynyl optionally substituted on the aryl ring by halogen, nitro, cyano, C_{1-6}alkylcarbonylamino, hydroxy or C_{1-6}alkoxy; or a five-membered aromatic ring containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, or a six-membered aromatic ring containing 1, 2, 3 or 4 nitrogen atoms, which ring is optionally substituted by halogen, C_{1-6}alkoxy, C_{1-6}alkylthio, aryl, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

R^2 and R^3 are independently hydrogen or C_{1-6}alkyl or together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group;

R^4 is hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl or $CH_2(CO)_mNR^8R^9$;

R^5 is NR^6R^7, C_{1-6}alkyl or C_{1-6}alkoxy;

R^6 is independently as defined for R^4;

R^7 is aryl optionally substituted by halogen, nitro or cyano;

R^8 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{2-6}alkenyl, C_{2-6}alkynyl; arylC_{1-6}alkyl, arylC_{2-6}alkenyl or arylC_{2-6}alkynyl optionally substituted on the aryl ring by halogen, nitro or cyano; thiophene or pyridine;

R^9 is C_{1-6}alkyl; C_{2-6}alkenyl; C_{2-6}alkynyl; or phenyl optionally substituted by one, two or three substituents independently chosen from halogen, CF_3, OCH_3, nitro and cyano;

R^{10} is hydrogen or C_{1-6} alkyl;

R^{14} is hydrogen or C_{1-6}alkyl;

m is zero or 1;

p is zero, 1 or 2;

q is 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2; and

t is 0, 1 or 2.

B may be phenyl or a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, or a 6-membered aromatic ring containing 1, 2, 3 or 4 nitrogen atoms, which ring is optionally substituted by one or more substituents independently chosen from: C_{1-6}alkyl; C_{1-6}haloalkyl; halogen; $S(O)_rR^4$; COR^5; and aryl or arylC_{1-6}alkyl wherein the aryl ring is optionally substituted by one, two or three substituents independently chosen from halogen, CF_3, OCH_3, nitro and cyano; and when a nitrogen ring atom is present it is optionally substituted by oxygen;

B is preferably an optionally substituted phenyl or optionally substituted 6-membered heteroaromatic ring. The optional substituents are preferably one or two groups independently chosen from halogen, C_{1-6}alkyl, trifluoromethyl, cyano and an unsubstituted 5-membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S in which not more than one heteroatom is other than N. The optional substituent is preferably chosen from halogen, C_{1-6}alkyl, trifluoromethyl and cyano.

B is most particularly optionally substituted phenyl or pyridine. In particular B may be pyridine and preferably pyridin-2-yl.

Thus when B is a heteroaromatic ring it may be a thiazole, pyrazole, pyrimidine, tetrazole, triazole, oxadiazole, oxazole, pyridine, imidazole or pyrazine which is unsubstituted or substituted by C_{1-6}alkyl, halogen, SR^4, COR^5 or benzyl optionally substituted by halogen. When B is a 5- or 6-membered ring having one unsaturation it is preferably oxazolidinyl or imidazolinyl optionally substituted by halogen or C_{1-4}alkyl.

Particular embodiments of B are (1-phenylsulphonyl)pyrazol-3-yl, 1-acetylpyrazol-3-yl, (3-ethoxycarbonyl)isoxazol-5-yl, (3-isopropyl)-1,2,4-oxadiazol-5-yl, imidazolin-2-yl, pyrazol-4-yl, 2-methyl-1,3,4-oxadiazol-5-yl, oxazolidin-2-yl, 2-methyltetrazol-5-yl, pyrazol-3-yl, 2-propyltetrazol-5-yl, thiazol-2-yl, 4-methyl-1,2,4-triazol-3-yl, (4-ethoxycarbonyl)thiazol-2-yl, (4-

trifluoromethyl)thiazol-2-yl, (4-acetyl)thiazol-2-yl, (4-methyl)thiazol-2-yl, pyrrol-2-yl, pyrid-2-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 4-benzyl-1,2,4-triazol-3-yl, 1-methyl-1,2,4-triazol-3-yl, oxazol-2-yl, pyrazin-2-yl, pyrimidin-5-yl, 3-(N-methylaminocarbonyl)thiazol-2-yl, thiazol-5-yl, isoxazol-5-yl, pyrid-3-yl, pyrid-4-yl, 1,3,4-oxadiazol-5-yl and 1-methylsulphonylpyrazol-3-yl.

Other particular embodiments of B are pyridin-2-yl, 6-methyl pyridin-2-yl, thiazol-2-yl, 4-chlorophenyl, 4-fluorophenyl, 3-fluorophenyl, 4-trifluoromethylphenyl, 4-methylphenyl, 3-methylphenyl, pyrimidin-2-yl, pyridin-3-yl, 2-cyanophenyl, 5-chloropyridin-2-yl and 6-(thiazol-2-yl) pyridin-2-yl.

R^1 is preferably C_{1-6}alkyl, C_{2-6}alkenyl or C_{3-6}cycloalkyl each of which is optionally substituted by amino, di(C_{1-6}alkyl)amino, hydroxy, C_{1-6}alkoxy, C_{1-6}alkylaminocarbonyl or one, two or three halogen atoms; aryl or arylC_{1-6}alkyl optionally substituted on the aryl ring by halogen, C_{1-6}alkylcarbonylamino or C_{1-6}alkoxy; or a five-membered aromatic ring containing 1, 2 or 3 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, or a six-membered aromatic ring containing 1 or 2 nitrogen atoms, which ring is optionally substituted by halogen, C_{1-6}alkoxy, C_{1-6}alkylthio, aryl or C_{1-6}alkyl.

More preferably R^1 is C_{1-6}alkyl, C_{1-4}alkenyl, or C_{3-6}cycloalkyl each of which is optionally substituted by di(C_{1-4}alkyl)amino, C_{1-4}alkoxy, C_{1-4}alkylaminocarbonyl, one or two hydroxy groups or three fluorine atoms; phenyl or phenylC_{1-4}alkyl optionally substituted on the phenyl ring by chlorine, fluorine, C_{1-4}alkoxy or C_{1-4}alkylcarbonylamino; or a pyridine, thiophene, furan, pyrimidine, thiazole, imidazole, triazole or thiadiazole, each of which is unsubstituted or substituted by C_{1-4}alkyl, phenyl, fluorine or C_{1-4}alkylthio. In particular R^1 is C_{1-6}alkyl, phenyl, benzyl or pyridyl.

A may be C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, arylC_{1-6}alkyl, aryl, $S(O)_pR^1$, heteroarylC_{1-6}alkyl or heteroaryl where heteroaryl is a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that

not more than one heteroatom is other than N, or a 6-membered aromatic ring containing 1, 2, 3 or 4 nitrogen atoms, which ring is optionally substituted by one or more substituents independently chosen from: C_{1-6}alkyl; C_{1-6}haloalkyl; halogen; $S(O)_rR^4$; COR^5; and aryl or aryl C_{1-6}alkyl wherein the aryl ring is optionally substituted by one, two or three substituents independently chosen from halogen, CF_3, OCH_3, nitro and cyano; and when a nitrogen ring atom is present it is optionally substituted by oxygen.

When A is not $S(O)_pR^1$ it is preferably C_{1-6}alkyl, C_{2-6}alkenyl or C_{3-6}cycloalkyl. A may be C_{1-6}alkyl such as ethyl.

A is preferably C_{1-6}alkyl, C_{2-6}alkenyl, arylC_{1-6}alkyl or aryl wherein the aryl group is optionally substituted by a halogen atom or a C_{1-6}alkyl group, a 5- or 6-membered heteroaromatic ring optionally substituted by a halogen atom or C_{1-6}alkyl, NHR^1 or SR^1.

Particular embodiments of A include ethyl, 1,1-dimethylethyl, cyclopropyl, thiazol-2-yl, ethylthio, benzyl, phenyl, methylthio, ethenyl, phenylamino, pyridin-2-ylamino, phenylthio, pyrid-2-yl, benzylthio, oxazol-2-yl, 3-methyl-1,2,4-oxadiazol-5-yl, thiazol-5-yl, 4-chlorophenyl, 4-methylthiazol-2-yl, 3-chlorophenyl and 2-chlorophenyl.

Particular embodiments of A are phenyl, cyclohexyl, 2-methylprop-1-enyl, methylthio, ethyl, isopropyl, propyl, cyclobutyl, but-3-enyl, cyclopropyl, methanesulphonyl, methyl, benzyl, methanesulphinyl, (1,1-dimethylethyl)thio, pentylthio, (4-methyl-1,2,4-triazol-3-yl)thio, hexylthio, benzylamino, (3-imidazol-1-ylpropyl)amino, (pyrid-2-yl)amino, 2-methylprop-1-yl, [3-(4-methylpiperazin-1-yl)propyl]amino, methylamino, (2-hydroxyethyl)amino, azetidin-1-yl, tert-butylamino, isopropylthio, (2-hydroxyethyl)thio, methoxy, dimethylamino, cyclobutoxy, phenoxy, butylthio, (3-chloropropyl)thio, (2-phenylethyl)thio, propylthio, (2-methylbutyl)thio, (2,2,2-trifluoroethyl)thio, (1-methylpropyl)thio, (4-chlorophenyl)thio, (3-fluorophenyl)thio, (4-acetylaminophenyl)thio, (4-methoxyphenyl)thio, (1-methylimidazol-2-yl)thio, (thiophen-2-yl)thio,

(imidazol-2-yl)thio, (4-phenylthiazol-2-yl)thio, (1,2,4-triazol-3-yl)thio, (5-methyl-1,3,4-thiadiazol-2-yl)thio, (5-methylthio-1,3,4-thiadiazol-2-yl)thio, benzylthio, cyclopentylthio, (2-methylpropyl)thio, (furan-2-ylmethyl)thio, (2-hydroxy-1-methylpropyl)thio, (2,3-dihydroxypropyl)thio, (2-hydroxypropyl)thio, ((N-methylaminocarbonyl)methyl)thio, (pyrid-4-yl)thio, (pyrimidin-2-yl)thio, (thiazol-2-yl)thio, prop-2-enylthio, (pyrid-2-yl)thio, ethylthio, phenylthio, (N,N-dimethyl-2-aminoethyl)thio, (2-methoxyethyl)thio, (furan-2-ylmethyl)amino, (2-methylpropyl)amino, propylamino, (2-methoxyethyl)amino, cyclopropylamino, isopropylamino, ethylamino, cyclobutylamino and isopropoxy.

When A is heteroaryl it may be a thiazole, pyrazole, pyrimidine, tetrazole, triazole, oxadiazole, oxazole, pyridine, imidazole or pyrazine.

R^2 and R^3 are preferably independently chosen from hydrogen, methyl and propyl or are attached to the same carbon atom and together with that atom form a C_{3-6}cycloalkyl group. Alternatively R^2 and R^3 are independently chosen from hydrogen and methyl. R^2 may be hydrogen with R^3 being hydrogen, methyl or isopropyl. Preferably both are methyl. Preferably R^2 and R^3 are geminal to each other, preferably at the 6-position, i.e. beta to the carbonyl group in formula I.

R^4 may by hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, aryl or $CH_2(CO)_mNR^8R^9$. R^4 is preferably hydrogen, C_{1-4}alkyl or $CH_2(CO)_mNR^8R^9$, more preferably hydrogen, methyl or $CH_2CONR^8R^9$ and most preferably methyl or $CH_2CONR^8R^9$.

R^5 is preferably methyl, methoxy, ethoxy or NR^6R^7 and most preferably methyl, ethoxy or NR^6R^7.

R^6 may be hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, aryl or $CH_2(CO)_mNR^8R^9$. R^6 is preferably hydrogen or C_{1-4}alkyl and most preferably hydrogen.

R^7 is preferably phenyl unsubstituted or substituted by halogen, nitro or cyano, more preferably optionally substituted by halogen, such as chlorine.

R^8 is preferably hydrogen or C_{1-6}alkyl and most preferably hydrogen.

R^9 is preferably C_{1-6}alkyl or phenyl unsubstituted or substituted by one, two or three substituents independently chosen from halogen, nitro and cyano, more preferably C_{1-6}alkyl or phenyl optionally substituted by one or two substituents independently chosen from halogen and nitro and most preferably *tert*-butyl or phenyl optionally substituted with one or two substituents chosen from chlorine and nitro, such as 4-chlorophenyl.

R^{10} is preferably hydrogen or methyl, particularly hydrogen.

R^{14} is generally hydrogen or C_{1-4}alkyl and most preferably hydrogen.

m is preferably 1.

p is preferably zero or two, most preferably zero.

q is preferably 1.

r is preferably 1.

s is preferably 0 or 1. s may be 1. s may be 0

t is preferably 0 or 1. t may be 1. t may be 0.

A specific Example of a compound according to the present invention is:

6,6-dimethyl 3-ethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one and the pharmaceutically acceptable salts thereof.

Further specific Examples of compounds according to the present invention are:

6,6-dimethyl-3-(1,1-dimethylethyl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

3-cyclopropyl-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

3-ethyl-6,6-dimethyl-1-(pyrimidin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

6,6-dimethyl-3-ethyl-1-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;

6,6-dimethyl-3-ethyl-1-(3-fluorophenyl)-4,5,6,7-tetrahydroindol-4-one;

6,6-dimethyl-3-ethyl-1-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-3-ethyl-1-(4-methylphenyl)-4,5,6,7-tetrahydroindol-4-one;
1-(4-chlorophenyl)-6,6-dimethyl-3-ethyl-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-3-ethyl-1-(4-fluorophenyl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-3-ethyl-1-(3-methylphenyl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-3-methylthio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-3-ethylthio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-3(phenylmethyl)thio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-1-(pyridin-2-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-3-phenyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-1-(pyridin-2-yl)-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-1-(pyridin-2-yl)-3-vinyl-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-3-phenylmethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-3-(oxazol-2-yl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-1-(pyridin-2-yl)-3-(thiazol-5-yl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-3-phenylamino-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-1-(pyridin-2-yl)-3-(pyridin-2-ylamino)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-3-ethyl-1-(6-methylpyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
6,6-dimethyl-3-(4-methylthiazol-5-yl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

3-(4-chlorophenyl)-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

3-(3-chlorophenyl)-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

3-(2-chlorophenyl)-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

6,6-dimethyl-1-(pyridin-3-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;

1-(5-chloropyridin-2-yl)-6,6-dimethyl-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;

6,6-dimethyl-3-(thiazol-2-yl)-1-(6-(thiazol-2-yl)pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

1-(2-cyanophenyl)-6,6-dimethyl-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;

and the pharmaceutically acceptable salts thereof.

Further specific compounds of the present invention are:

6,6-dimethyl-3-ethyl-1-(6-methylpyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

6,6-dimethyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

6,6-dimethyl-3-(3-methylthiazol-5-yl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

3-(1,1-dimethylethyl)-6-methyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

3-ethyl-6-methyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

6-methyl-1-(pyridin-2-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;

3-(1,1-dimethylethyl)-6-(2-methylethyl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

1-(pyridin-2-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;

and the pharmaceutically acceptable salts thereof.

There is also provided a pharmaceutical composition comprising a compound of formula I according to the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Preferably the compositions according to the present invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, by inhalation or insufflation or administration by trans-dermal patches or by buccal cavity absorption wafers.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials

including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, peanut oil or soybean oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

Compositions of the present invention may also be presented for administration in the form of trans-dermal patches using conventional technology. The compositions may also be administered via the buccal cavity using, for example, absorption wafers.

In disorders associated with $GABA_A$ α receptors, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100

mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The present invention also provides a process for the preparation of a pharmaceutical composition which comprises adding a compound of formula (I) or a pharmaceutically acceptable salt thereof to a pharmaceutically acceptable excipient.

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in a method of treatment of the human or animal body, in particular for the treatment or prevention of conditions for which the administration of a cognition enhancing agent is desirable, such as Alzheimer's disease.

The compounds of formula (I) are of potential value in the treatment or prevention of a wide variety of clinical conditions which can be alleviated by a ligand selective for $GABA_A$ receptors containing the $\alpha5$ subunit. In particular, they are desirably inverse agonists of the $\alpha5$ subunit.

Thus, for example, such a ligand can be used in a variety of disorders of the central nervous system. Such disorders include delirium, dementia and amnestic and other cognitive disorders. Examples of delirium are delirium due to substance intoxication or substance withdrawal, delirium due to multiple etiologies and delirium NOS (not otherwise specified). Examples of dementia are: dementia of the Alzheimer's type with early onset which can be uncomplicated or with delirium, delusions or depressed mood; dementia of the Alzheimer's type, with late onset, which can be uncomplicated or with delirium, delusions or depressed mood; vascular dementia which can be uncomplicated or with delirium, delusions or depressed mood; dementia due to HIV disease; dementia due to head trauma; dementia due to Parkinson's disease; dementia due to Huntington's disease; dementia due to Pick's disease; dementia due to Creutzfeld-Jakob disease; dementia which is substance-induced persisting or due to multiple etiologies; and dementia NOS.

Examples of amnestic disorders are amnestic disorder due to a particular medical condition or which is substance-induced persisting or which is amnestic disorder NOS. In particular the compounds of formula (I) may be of use in conditions which require cognition enhancement.

Where the compounds of the present invention are selective ligands for $GABA_A$ $\alpha2$ or $\alpha3$ subtype receptors they may be used in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine; and depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder.

The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of a condition requiring the administration of a ligand selective for $GABA_A$ receptors containing the $\alpha5$ subunit, in particular for conditions requiring cognition enhancement such as Alzheimer's disease. Other conditions to be treated include cognition deficits due to traumatic injury, stroke, Parkinson's disease, Downs syndrome, age related memory deficits, attention deficit disorder and the like.

There is also disclosed a method of treatment or prevention of a condition associated with $GABA_A$ receptors containing the $\alpha5$ subunit in a subject suffering from or prone to such a condition which comprises administering to that subject a therapeutically or prophylactically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. In particular there is disclosed the treatment and

prevention of conditions which require the administration of a cognition enhancing agent, such as Alzheimer's disease.

As used herein, the expression "C_{1-6}alkyl" includes methyl and ethyl groups, and straight-chained and branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "C_{2-6}alkenyl", "C_{2-6}alkynyl", "C_{1-4}alkyl", "C_{2-4}alkenyl" and "C_{2-4}alkynyl" are to be construed in an analogous manner.

The expression "C_{3-6}cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. "C_{5-6}cycloalkenyl", "C_{3-8}cycloalkyl" and "C_{5-7}cycloalkyl" are to be construed analogously.

Suitable 5- and 6-membered heteroaromatic rings include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, thienyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, isothiazolyl, imidazolyl, tetrazolyl, oxadiazolyl and thiadiazolyl groups. These rings also include thiazolyl and triazolyl groups.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine, chlorine and bromine.

The expression "arylC_{1-6}alkyl" as used herein includes benzyl, phenylethyl, phenylpropyl and naphthylmethyl. "ArylC_{2-6}alkenyl", "arylC_{2-6}alkynyl" and "heteroarylC_{1-6}alkyl" should be construed in an analogous fashion.

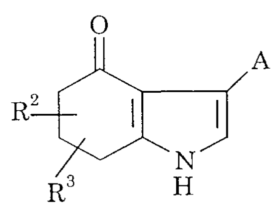
Typical aryl groups include phenyl and naphthyl. Preferably the aryl is phenyl.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable

acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

Where the compounds of formula (I) have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds of formula (I) possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

The present invention also provides a process for producing a compound of formula I which comprises reacting a compound of formula II with a compound of formula III:



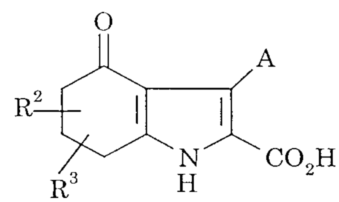
(II)

Hal-B

(III)

wherein R^2, R^3, A and B are as defined above and Hal is a halogen atom such as bromine, chlorine or fluorine, generally in a solvent such as DMF and in the presence of a strong base such as NaH, generally with heating to about 90^{0}C for about 6 h. Alternatively the reaction may be carried out using CuBr in DMF in the presence of K_2CO_3 generally with heating to about 180°C for about 48h.

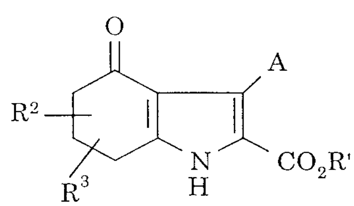
The compound of formula II is prepared by decarboxylating a compound of formula IV:



(IV)

wherein R^2 and R^3 are as defined above by heating at about 100^0C for about 45 minutes generally in the presence of an acid such as acetic acid and/or hydrochloric acid.

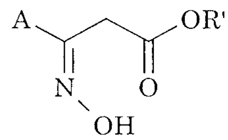
The compounds of formula IV is prepared by hydrolysing a compound of formula V:



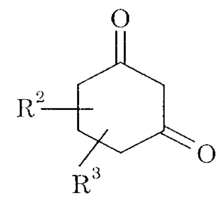
(V)

wherein R^2 and R^3 are as defined above generally by heating at reflux for about 6h generally in the presence of a base such as KOH and a solvent such as ethanol and water. This reaction can also be performed by heating the compound of formula V in DMSO and H_2O at about 150°C for about 18h.

The compound of formula V is prepared by reacting a compound of formula VI with a compound formula VII:



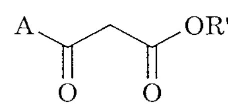
(VI)



(VII)

wherein A and R^1 are defined above, generally with heating to about 100°C for about 1h in a buffered solution such as acetic acid/sodium acetate in the presence of a catalyst such as zinc optionally in powdered form. This reaction can produce a compound of formula II directly when it is carried out at about 150°C.

The compound of formula VI is prepared by reacting a compound of formula VIII:

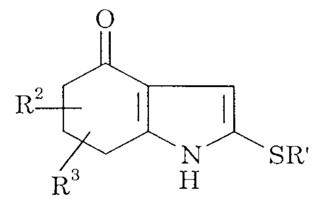


(VIII)

wherein A and R′ are as defined above, with sodium nitrite generally in the presence of an acid such as acetic acid in a solvent such as water at room temperature for about 1h.

The compounds of formulae III, VII and VIII are either commercially available or can be made by the skilled person from commercially available compounds by known methods.

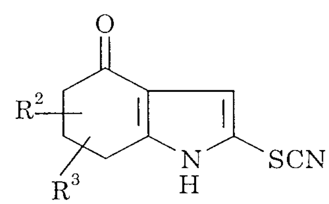
In an alternative process, a compound of formula II in which A is SR^1, wherein R^1 is as defined above, is prepared by reacting a compound of formula IX:



(IX)

wherein R^2 and R^3 are as defined above, with heating for about four hours in the presence of an acid such as trifluoroacetic acid, generally in a solvent such as $ClCH_2CH_2Cl$. The resulting product is a mixture of compounds of formulae II and IX which are then separated by conventional means.

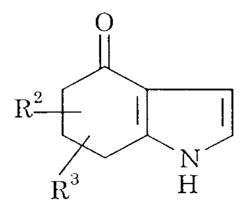
The compound of formula IX is prepared by reacting a compound of formula X:



(X)

wherein R^2 and R^3 are as defined above, with R^1I, wherein R^1 is as defined above, in the presence of a solvent such as methanol with a base as ROH for about 3h at room temperature. The compound R^1I is commercially available or may be made by methods known to the skilled person from commercially available compounds.

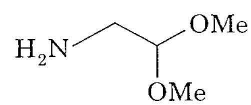
The compound of formula X is made by reacting a compound of formula XI:



(XI)

wherein R^2 and R^3 are as defined above, with bromine and KSCN in a solvent such as methanol at a temperature of from - 30°C to room temperature.

The compound of formula XI can be made by reacting a compound of formula VII with a compound of formula XII:



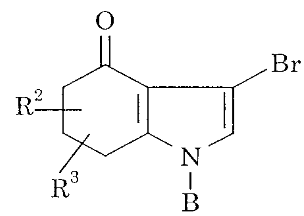
(XII)

with paratoluensulphonic acid generally in a solvent such as toluene with heating for about 3 h, and then carrying out a Michael addition by heating at about 40°C for about 9 h with an acid such as HCl, preferably at 3N.

The compound of formula XII is commercially available or can be made by known methods from commercially available compounds.

Alternatively the compound of formula XI may be obtained commercially.

Alternatively a compound of formula I is produced by reacting a compound of formula XIII with a compound of formula XIV:



Z - A

(XIII) (XIV)

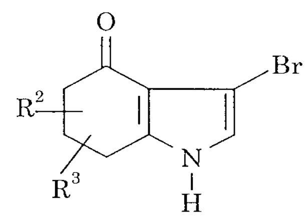
wherein R^2, R^3, A and B are as defined above:

(i) where Z is $Sn(Bu)_3$ in the presence of tetrakis(triphenylphosphene) palladium or dichlorobis(triphenylphosphine) palladium in a solvent such as dioxan generally with heating to reflux in a solvent such as dioxan or hexamethylphosphoramide for about 24h to 48h at about 70°C;

(ii) where Z is $B(OH)_2$ in the presence of tetrakis(triphenylphosphene) palladium generally in a biphasic mixture of solvents such as ethylene glycol dimethyl ether and water and in the presence of a mild base such as Cs_2CO_3 or Na_2CO_3 at reflux for about 8h; or in the presence of $Cu(OAc)_2$ in a solvent such as DCM, in the presence of a base such as Et_3N generally at room temperature;

(iii) where Z is $NR^{10}H$ in the presence of tris(dibenzylideneacetone)dipalladium generally with a base such as NaO^tBu, a solvent such as toluene and a compound such as (R)-(+)-2,2′-bis(diphenylphosphino)-1,1-binaphthyl generally at reflux for about 3h. (This last method produces compounds of formula I in which A is NR^1R^{10}).

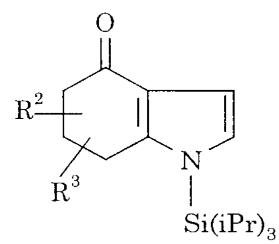
The compound of formula XIII can be produced by reacting a compound of formula XV:



(XV)

wherein R^2 and R^3 are as defined above with a compound of formula III as defined above generally in the presence of a strong base such as NaH and in a solvent such as DMF for about 5 min.

The compound of formula XV can be produced by reacting a compound of formula XVI:



(XVI)

wherein R^2 and R^3 are as defined above with a brominating agent such as N-bromosuccinimide generally in a solvent such as THF generally with cooling to about -78°C for about 1h.

The compound of formula XVI can be produced by reacting a compound of formula XI as defined above with $(^iPr)_3SiCl$ generally in a solvent such as DMF at about 0°C for about 1h.

Compounds of formula XIV are commercially available or can be made by known by methods from commercially available compounds.

A compound of formula I may also be prepared by interconversion from another compound of formula I by known methods.

Compounds of formula I in which A is $S(O)_pR^1$ wherein p is one or two can be obtained by reacting a compound of formula I in which A is S(O)pR^1 in which p is zero or one and R^1 is as defined above with a

stoichiometric quantity of mCPBA, generally in a solvent such as CH_2Cl_2: dioxan with cooling to about -78^{0}C.

It will be understood that the above transformations of $S(O)_pR^1$ are illustrative and other standard techniques known to the skilled person may alternatively be used.

The following Examples illustrate pharmaceutical compositions according to the invention.

COMPOSITION EXAMPLE 1A Tablets containing 1-25mg of compound

	Amount mg		
Active Ingredients(s)	1.0	2.0	25.0
Microcrystalline cellulose	20.0	20.0	20.0
Modified food corn starch	20.0	20.0	20.0
Lactose	58.5	57.5	34.5
Magnesium Stearate	0.5	0.5	0.5

COMPOSITION EXAMPLE 1B Tablets containing 26-100mg of compound

	Amount mg		
Active Ingredients(s)	26.0	50.0	100.0
Microcrystalline cellulose	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	213.5	189.5	139.5
Magnesium Stearate	0.5	0.5	0.5

The active ingredient(s), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.

COMPOSITION EXAMPLE 2 Parenteral injection

	Amount
Active Ingredient(s)	1 to 100mg
Citric Acid Monohydrate	0.75mg
Sodium Phosphate	4.5mg
Sodium Chloride	9mg
Water for injection	to 10ml

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The active ingredient(s) is (are) dissolved or suspended in the solution and made up to volume.

COMPOSITION EXAMPLE 3 Topical formulation

	Amount
Active Ingredient(s)	1-10g
Emulsifying Wax	30g
Liquid paraffin	20g
White Soft Paraffin	to 100g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient(s) is (are) is added and stirring continued until dispersed. The mixture is then cooled until solid.

The following Examples illustrate the compounds of the present invention.

The compounds in accordance with this invention potently inhibit the binding of [^{3}H]-flumazenil to the benzodiazepine binding site of human $GABA_A$ receptors containing the α5 subunit stably expressed in Ltk$^-$ cells.

Reagents

- Phosphate buffered saline (PBS).
- Assay buffer: 10 mM KH_2PO_4, 100 mM KCl, pH 7.4 at room temperature.
- [^{3}H]-Flumazenil (18 nM for $\alpha1\beta3\gamma2$ cells; 18 nM for $\alpha2\beta3\gamma2$ cells; 10 nM for $\alpha3\beta3\gamma2$ cells; 10 nM for $\alpha5\beta3\gamma2$ cells) in assay buffer.
- Flunitrazepam 100 μM in assay buffer.
- Cells resuspended in assay buffer (1 tray to 10 ml).

Harvesting Cells

Supernatant is removed from cells. PBS (approximately 20 ml) is added. The cells are scraped and placed in a 50 ml centrifuge tube. The procedure is repeated with a further 10 ml of PBS to ensure that most of the cells are removed. The cells are pelleted by centrifuging for 20 min at 3000 rpm in a benchtop centrifuge, and then frozen if desired. The pellets are resuspended in 10 ml of buffer per tray (25 cm x 25 cm) of cells.

Assay

Can be carried out in deep 96-well plates or in tubes. Each tube contains:

- 300 μl of assay buffer.
- 50 μl of [^{3}H]-flumazenil (final concentration for $\alpha 1\beta 3\gamma 2$: 1.8 nM; for $\alpha 2\beta 3\gamma 2$: 1.8 nM; for $\alpha 3\beta 3\gamma 2$: 1.0 nM; for $\alpha 5\beta 3\gamma 2$: 1.0 nM).
- 50 μl of buffer or solvent carrier (e.g. 10% DMSO) if compounds are dissolved in 10% DMSO (total); test compound or flunitrazepam (to determine non-specific binding), 10 μM final concentration.
- 100 μl of cells.

Assays are incubated for 1 hour at 40°C, then filtered using either a Tomtec or Brandel cell harvester onto GF/B filters followed by 3 x 3 ml washes with ice cold assay buffer. Filters are dried and counted by liquid scintillation counting. Expected values for total binding are 3000-4000 dpm for total counts and less than 200 dpm for non-specific binding if using liquid scintillation counting, or 1500-2000 dpm for total counts and less than 200 dpm for non-specific binding if counting with meltilex solid scintillate. Binding parameters are determined by non-linear least squares regression analysis, from which the inhibition constant K_i can be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K_i value for displacement of [^{3}H]Ro 15-1788 from the $\alpha 5$ subunit of the human $GABA_A$ receptor of 500 nM or less, preferably of 100 nM or less, and more particularly of 50 nM or less.

More preferably the compounds of the present invention are inverse agonists at the $GABA_A$ $\alpha 5$ subtype whilst being substantially antagonists at the α_1, α_2 and α_3 subtypes. Details of how the effects at the various subtypes can be measured are given in WO-A-9625948.

Further, the present compounds preferably bind preferentially to the $GABA_A$ $\alpha 5$ subtype when compared with the α_1, α_2 and α_3 subtypes.

The preferential binding is preferably 5-fold, more preferably 10-fold and most preferably 20-fold.

Intermediate 1

6,6-Dimethyl 3-ethyl-4,5,6,7-tetrahydro-1H-indol-4-one

Step 1: Ethyl 6,6-dimethyl 3-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate

Ethyl propionylacetate (15g, 0.1mol) and acetic acid (40mL) were cooled to 10^0C, and a solution of sodium nitrite (10.4g, 0.15mol) in water (40mL) was added dropwise to the stirred mixture maintaining the temperature below 20^0C. After addition the mixture was warmed to room temperature and stirred for 1h. The mixture was then extracted with CH_2Cl_2 (3 x 100mL) and washed with water (100mL), $NaHCO_3$ (10% (^{W}/v), 100mL) and water (100mL). The organic layer was separated dried (MgSO4) and evaporated to afford the oxime (13.2g, 73%) as a yellow oil which solidified on standing. The oxime was used without further purification. ^{1}H NMR (360MHz, d_6-DMSO) δ 1.01 (3H,t,J=7.3Hz), 1.23 (3H,t,J=7.1Hz), 2.80 (2H,q,J=7.3Hz), 4.24 (2H,q,J=7.1Hz), 13.16 (1H,br s).

Sodium acetate trihydrate (7.8g, 0.057 mol) and 5,5-dimethyl-1,3-cyclohexandione (10.7g, 0.076mol) in acetic acid (90mL) were heated to 70^0C. A solution of the oxime (13.2g, 0.076mol) in acetic acid (45mL) was added portionwise whilst simultaneously adding zinc dust (8g), over a period of 30 min, maintaining the temperature between 70-80^0C. The solution was then heated at 100^0C for 1h, cooled to 70^0C, then water (20mL) was added and heating continued at 100^0C for 6h. The solution was then cooled to room temperature, poured into ice-water (400mL) and extracted with CH_2Cl_2 (3 x 200mL). The combined organic layers were washed with water (200mL), separated, dried ($MgSO_4$) and evaporated.

The residue was chromatographed on silica gel (hexane:EtOAc 4:1→1:1) and the fractions containing the desired product were combined and evaporated. The resultant orange solid was recrystallized from MeOH (30ml) to afford the pyrrole (5.7g, 28%) as a yellow solid. mp 163-166^{0}C. ^{1}H NMR (360MHz, d_6-DMSO) δ 1.00 (6H,s), 1.06 (3H,t,J=7.3Hz), 1.29 (3H,t,J=7.1Hz), 2.23 (2H,s), 2.64 (2H,s), 2.98 (2H,q,J=7.3Hz), 4.25 (2H,q,J=7.1Hz), 11.86 (1H,s). MS(ES$^+$) 264 (M+1).
$C_{15}H_{21}NO_3$ requires: C, 68.42; H, 8.04; N, 5.32%. Found: C, 68.55; H, 8.12; N, 5.27%.

Step 2: 6,6-Dimethyl 3-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid

A solution of ethyl 6,6-dimethyl-3-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (5.4g, 0.02mol) and KOH (2.9g, 0.05mol) in EtOH (25mL) and water (7.5mL) was heated at reflux for 6h. The mixture was cooled to 60^{0}C, and neutralized by the addition of acetic acid. Water (80mL) was added and the cream precipitate collected by filtration. The precipitate was washed with EtOH and hexane then dried under vacuum at 50^{0}C. The acid (4g, 83%) was isolated as a cream solid, and used without further purification. mp > 198°C. ^{1}H NMR (360MHz, d_6-DMSO δ 1.00 (6H,s), 1.04 (3H,t,J=7.3Hz), 2.22 (2H,s), 2.62 (2H,s), 2.98 (2H,q,J=7.3Hz), 11.72 (1H, br s).
$C_{13}H_{17}NO_3$. O.4(H_2O) requires: C, 64.39; H, 7.40; N, 5.73%. Found:C, 64.38, H, 7.30; N, 5.70%. MS(ES$^+$) 236 (M+1).

Step 3: 6,6-Dimethyl-3-ethyl-4,5,6,7-tetrahydro-1H-indol-4-one

A suspension of 6,6-dimethyl-3-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid (2.5g, 0.011mol) in acetic acid (12mL) and hydrochloric acid (10M; 0.64mL) was heated at 100^0C for 45 min. After this time water (50mL) was added, the cooling bath removed and the solution stirred at room temperature for 2h. The precipitate was collected by filtration and the title pyrrole (1.76g, 87%) isolated as a colourless solid. mp. 150°C-152°C. $C_{12}H_{17}NO$ requires: C, 75.35; H, 8.96; N, 7.32%. Found: C, 75.00; H, 8.88; N, 7.24%. ^{1}H NMR (250MHz, $CDCl_3$) δ 1.10 (6H,s), 1.19 (3H,t,J=7.4Hz), 2.32 (2H,s), 2.63 (2H,s), 2.75 (2H,d of q,J=7.4 and 1.0Hz), 6.42 (1H,br s), 8.00 (1H,br s). MS (ES^+) 192 (M+1).

Example 1

6,6-Dimethyl 3-Ethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

To a solution of 6,6-dimethyl 3-ethyl-4,5,6,7-tetrahydro-1H-indol-4-one (50mg, 0.26mmol) in DMF (4mL) at 0^0C, was added NaH (11mg of a 60% dispersion in mineral oil, 0.29mmol). The cooling bath was removed and the mixture stirred at room temperature for 20 min. After this time 2-fluoropyridine (26μl, 0.29mmol) was added and the residue heated at 90^0C for 6h. The solvent was evaporated and the residue partitioned between EtOAc (20mL) and water (20mL). The organic layer was separated, dried (Na_2SO_4) and evaporated. The residue was chromatographed an silica gel, eluting with hexane:EtOAc (2:1), to give the title pyrrole (18mg, 26%) as a colourless solid. mp125-127^0C ^{1}H NMR (360MHz, $CDCl_3$) δ 1.10 (6H,s), 1.23 (3H,t,J=7.4Hz), 2.38 (2H,s), 2.83 (2H,d of q, J=7.4 and 1.0Hz), 2.92 (2H,s), 6.88 (1H,s), 7.25-7.27 (1H,m), 7.30 (1H,d,J=8.0Hz), 7.82 (1H,d of t, J=7.7 and 1.9Hz), 8.51 - 8.57 (1H,m). MS (ES^+) 269 (M+1).

Example 2

6,6-Dimethyl-3-(1,1-dimethylethyl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

Step 1: 6,6-Dimethyl-3-(1,1-dimethylethyl)-4,5,6,7-tetrahydro-1H-indol-4-one

Methyl 4,4-dimethyl-3-oxopentanoate (20g, 0.13mol) and AcOH (48mL) were cooled to 10°C and a solution of $NaNO_2$ (12.3g, 0.19mol) in water (48mL) was added dropwise to the stirred mixture, maintaining the temperature below 20°C. After addition the mixture was warmed to room temperature and stirred for 2h. The mixture was then extracted with DCM (3x100mL). The combined organic layers were evaporated and the residue taken up in ether. The ethereal layer was washed with water (100mL), separated and dried (Na_2SO_4). The resultant yellow gum (22.7g, 96%) was used without further purification. ^1H NMR (250MHz, $CDCl_3$) δ 1.23 (9H,s), 3.89 (3H,s), 9.00 – 10.00 (1H,br s). Sodium acetate trihydrate (20.6g, 0.15mol) and 5,5-dimethyl-1,3-cyclohexandione (16.9g, 0.12mol) in propionic acid (140mL) were heated to 150°C. A solution of the oxime (22.7g, 0.12mol) in propionic acid (70mL) was added via a dropping funnel, whilst simultaneously adding zinc dust (12g) over 20 min. The solution was heated at reflux for 24h after which time it was poured into water. The resultant solid was collected by filtration then triturated with ether. The colourless solid (3.7g, 14%) was collected by filtration. ^1H NMR (360MHz, $CDCl_3$) δ 1.10 (6H,s), 1.35 (9H,s), 2.35 (2H,s), 2.64 (2H,s), 6.43 (1H,d,J=2.2Hz), 7.80 – 8.14 (1H,br s). MS (ES^+) 220 (M+1).

Step 2: 6,6-Dimethyl-3-(1,1-dimethylethyl)-1-(pyridin-2-yl)-4,5,6,7-1H-tetrahydroindol-4-one

In the same was as described in Example 1 using 6,6-dimethyl-3-(1,1-dimethylethyl)-4,5,6,7-1H-tetrahydroindol-4-one the title compound (24mg, 35%) was isolated as a colourless solid. mp 143-145°C. ^1H NMR (360MHz, $CDCl_3$) δ 1.08 (6H,s), 1.39 (9H,s), 2.40 (2H,s), 2.89 (2H,s), 6.87 (1H,s), 7.25 – 7.32 (2H,m), 7.83 (1H,d of t, J=7.8 and 2.0 H_2), 8.54 – 8.60 (1H,m). MS (ES^+) 297 (M+1).

Example 3

3-Cyclopropyl-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

Step 1: Methyl 3-cyclopropyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate

Methyl 4-cyclopropyl-3-oxobutanoate (15g, 0.106mol) in AcOH (40mL) was cooled to 10°C and a solution of $NaNO_2$ (9.9g, 0.14mol) in water (40mL) was added dropwise, maintaining the temperature below 20°C. After addition the mixture was warmed to 20°C, stirred for 90 min then washed with DCM (3x100mL). The aqueous phase was separated, evaporated and the residue triturated with ether. The resultant solid was filtered off and the filtrate evaporated to afford a yellow oil. The oil was dissolved in ether, washed with water (100mL) then the organic layer dried ($MgSO_4$) and evaporated. The oxime (18g, 100%) was isolated as a yellow oil and used without further purification. ^1H NMR (360MHz, d_6-DMSO) δ 0.97 – 1.08 (4H,m), 2.69 – 2.79 (1H,m), 3.76 (3H,s). 12.80 – 13.40 (1H,br s).

Sodium acetate trihydrate (17g, 0.13 mol) and 5,5-dimethyl-1,3-cyclohexandione (14g, 0.1 mol) in AcOH (117mL) was heated to 70°C. A

solution of the oxime (18g, 0.1 mol) in AcOH (58mL) was added via a dropping funnel, whilst simultaneously adding zinc dust (10g) over a period of 15 min, maintaining the temperature between 70 -80°C. The solution was heated at 100°C for 2h, after which time the mixture was cooled to room temperature, poured into ice-water (400mL) and extracted with DCM (3x100mL). The combined organic layers were washed with water (200mL), dried ($MgSO_4$) and evaporated. The resultant yellow oil solidified on standing at 0°C, whereupon isohexane/ether was added and the resultant pyrrole (6.5g, 25%) isolated as a colourless solid. ^1H NMR (360MHz, $CDCl_3$) δ 0.89 – 0.93 (2H,m), 1.09 (6H,s), 1.21 – 1.26 (2H,m), 2.33 (2H,s) 2.53 – 2.65 (3H,m) 3.87 (3H,s), 8.90 – 9.06 (1H,br s). MS (ES^+) 262 (M+1).

<u>Step 2: 3-Cyclopropyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid</u>

In the same way as described for Intermediate 1, Step 2, using methyl 3-cyclopropyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate the acid (3.8g, 100%) was isolated as a colourless solid. ^1H NMR (250 MHz, d_6-DMSO) δ 0.70 – 0.79 (2H,m), 1.00 (6H,s), 1.18 – 1.28 (2H,m), 2.22 (2H,s), 2.63 (2H,s), 2.74 – 2.86 (1H,m), 11.74 – 11.82 (1H,br s). MS (ES^+) 248 (M+1).

<u>Step 3: 3-Cyclopropyl-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one</u>

A solution of the acid (511mg, 2.1mmol) in DMSO (8mL) and water (2mL) was heated at 150°C for 18h. After this time the mixture was diluted with EtOAc (50mL) and washed with water (2x50mL). The organic layer was separated, dried (Na_2SO_4) and evaporated. The residue was triturated with ether/hexane to afford the title pyrrole (197mg, 47%) as a colourless solid. ^1H NMR (250MHz, $CDCl_3$) δ 0.45 –

0.52 (2H,m), 0.84 – 0.91 (2H,m), 1.10 (6H,s), 2.26 – 2.35 (3H,m), 2.61 (2H,s), 6.23 (1H,d, J = 3Hz), 7.94 – 8.22 (1H,br s). MS(ES^+) 204 (M+1).

Step 4: 3-Cyclopropyl-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described for example 1 using 3-cyclopropyl-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one the title compound (38mg, 41%) was isolated as a colourless solid. ^{1}H NMR (360MHz, $CDCl_3$) δ 0.53 – 0.57 (2H,m), 0.90 – 0.94 (2H,m), 1.10 (6H,s), 2.38 – 2.43 (3H,m), 2.91 (2H,s), 6.68 (1H,s), 7.22 – 7.27 (2H,m), 7.81 (1H,d of t, J = 8.1 and 2.0Hz), 8.50 – 8.55 (1H,m). MS (ES^+) 281 (M+1).

Example 4

3-Ethyl-6,6-dimethyl-1-(pyrimidin-2-yl)-4,5,6,7-tetrahydroindol-4-one

A solution of 6,6-dimethyl-3-ethyl-4,5,6,7-tetrahydro-1H-indole-4-one (100mg, 0.52mmol), K_2CO_3 (87mg, 0.63mmol), copper (I) bromide (15mg, 0.1mmol) and 2-chloropyrimidine (71mg, 0.63mmol) in DMF (1mL) were heated at 180°C for 24h. More copper (I) bromide (15mg, 0.1mmol) and 2-chloropyrimidine (50mg) were added and heating continued for a further 24h. The DMF was evaporated and the residue partitioned between water and DCM. The organic layer was separated and the aqueous phase extracted with DCM (2x). The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel, eluting with 4:1 isohexane: EtOAc, to afford the title compound (35mg, 25%) as a yellow solid. mp 111-114°C. Found: C, 71.07; H, 6.98; N, 15.20%. Calc $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60%. ^{1}H NMR (360MHz, d_6-DMSO) δ 1.06 (6H,s), 1.15 (3H,t, J = 7.4Hz), 2.30 (2H,s), 2.67 (2H,q, J = 7.3Hz), 3.23 (2H,s), 7.44

(1H,t, J = 4.8Hz), 7.47 (1H,s), 8.86 (2H,d, J = 4.8Hz). MS (ES^+) 270 (M+1).

Example 5

6,6-Dimethyl-3-ethyl-1-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described for Example 4 using 2-bromothiazole, the title compound (45mg, 31%) was isolated as a cream solid. mp 58-60°C. Found: C, 64.94; H, 6.25; N, 10.27%. Calc. $C_{15}H_{18}N_2OS.0.1(H_2O)$: C, 65.23, H, 6.64; N, 10.14%. ^1H NMR (360MHz, d_6-DMSO) δ 1.06 (6H,s), 1.15 (3H,t, J = 7.4Hz), 2.31 (2H,s), 2.66 (2H,q, J = 7.4Hz), 3.01 (2H,s), 7.14 (1H,s) 7.64 (1H,d, J = 3.5Hz), 7.71 (1H,d, J = 3.5Hz). MS (ES^+) 275 (M+1).

Example 6

6,6-Dimethyl-3-ethyl-1-(3-fluorophenyl)-4,5,6,7-tetrahydroindol-4-one

6,6-Dimethyl-3-ethyl-4,5,6,7-tetrahydro-1H-indol-4-one (50mg, 0.26mmol), copper acetate (71mg, 0.39mmol), 3-fluorophenyl boronic acid (73mg, 0.52mmol) and triethylamine (73μL, 0.52mmol) and triethylamine (73μL, 0.52mmol) in DCM (1mL) was stirred at room temperature for 48h. The crude reaction mixture was poured onto a bond elut tube (Anachem 1225-6034 10g/60mL) and eluted using isohexane : EtOAc (100:0 → 5:1) to afford a yellow solid. The solid was triturated in ether to afford the title compound (15mg, 20%) as a colourless solid. ^1H NMR (360MHz, $CDCl_3$) δ 1.08 (6H,s), 1.22 (3H,t, J = 7.4Hz), 2.36 (2H,s), 2.62 (2H,s), 2.81 (2H,q, J = 7.4Hz), 6.57 (1H,s), 7.02 – 7.11 (3H,m), 7.41 – 7.45 (1H,m). MS (ES^+) 286 (M+1).

Example 7

6,6-Dimethyl-3-ethyl-1-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 6 using 4-trifluoromethylbenzene boronic acid, the title compound (13mg, 10%) was isolated as a colourless solid. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.08 (6M,s), 1.23 (3H,t, J = 7.4Hz), 2.38 (2H,s), 2.64 (2H,s), 2.82 (2H,q, J = 7.4Hz), 6.60 (1H,s), 7.41 (2H,d, J = 8.4Hz), 7.75 (2H,d, J = 8.4Hz). MS (ES^+) 336 (M+1).

Example 8

6,6-Dimethyl-3-ethyl-1-(4-methylphenyl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 6 using 4-methylbenzene boronic acid, the title compound (65mg, 59%) was isolated as a colourless solid. Found: C, 80.53; H, 8.30; N, 4.76%. Calc. $C_{19}H_{23}NO.0.15(H_2O)$: C, 80.33; H, 8.27; N, 4.93%. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.06 (6H,s), 1.22 (2H,t, J = 7.4Hz), 2.27 (2H,s), 2.35 (3,H,s), 2.58 (2H,s), 2.80 (2H,q, J = 7.4Hz), 6.53 (1H,s), 7.17 (2H,d, J = 8.3Hz), 7.26 (2H,d, J = 8.3Hz). MS (ES^+) 282 (M+1).

Example 9

1-(4-Chlorophenyl)-6,6-dimethyl-3-ethyl-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 6 using 4-chlorobenzene boronic acid, the title compound (38mg, 32%) was isolated as a colourless solid. Found: C, 70.18; H, 6.58; N, 4.43%. Calc. $C_{18}H_{20}ClNO.0.4(H_2O)$:

C, 69.96; H, 6.78; N, 4.53%. ^1H NMR (360MHz, $CDCl_3$) δ 1.07 (6H,s), 1.22 (3H,t, J = 7.4Hz), 2.30 (2H,s), 2.58 (2H,s), 2.80 (2H,q, J = 7.4Hz), 6.54 (1H,s), 7.24 (1H,d, J = 8.7Hz), 7.44 (1H,d, J = 8.7Hz). MS (ES^+) 302/304 (M+1).

Example 10

6,6-Dimethyl-3-ethyl-1-(4-fluorophenyl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 6 using 4-fluorobenzene boronic acid, the title compound (50mg, 45%) was isolated as a colourless solid. Found: C, 74.76; H, 6.98; N, 4.80%. Calc. $C_{18}H_{20}FNO.0.2(H_2O)$: C, 74.82; H, 7.12; N, 4.85%. ^1H NMR (360MHz, d_6-DMSO) δ 0.99 (6H,s), 1.15 (3H,t, J = 7.5Hz), 2.25 (2H,s), 2.63 (2H,s), 2.66 (2H,q, J = 7.5Hz), 6.79 (1H,s), 7.37 (2H,dd, J = 8.7 and 8.7Hz), 7.49 (2H,dd, J = 8.7 and 4.9Hz). MS (ES^+) 286 (M+1).

Example 11

6,6-Dimethyl-3-ethyl-1-(3-methylphenyl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 6 using 3-methylbenzene boronic acid, the title compound (50mg, 31%) was isolated as a colourless solid. ^1H NMR (360MHz, $CDCl_3$) δ 1.07 (6H,s), 1.23 (3H,t, J = 7.5Hz), 2.31 (2H,s), 2.43 (3H,s), 2.59 (2H,s), 2.81 (2H,q, J = 7.5Hz), 6.55 (1H,s), 7.07 – 7.11 (2H,m), 7.19 (1H,d, J = 7.5Hz). 7.35 (1H,dd, J = 7.6 and 7.6Hz). MS (ES^+) 282 (M+1).

Example 12

6,6-Dimethyl-3-methylthio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

Step 1: 6,6-Dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one

A solution of 5,5-dimethyl-1,3-cyclohexandione (30g, 0.21mol), aminoacetaldehyde dimethyl acetal (35mL, 0.32mol) and p-toluenesulphonic acid hydrate (1.5g, 8mmol) in toluene (250mL) were heated at reflux for 4h using Dean-Stark apparatus to remove the water. The toluene was evaporated and the residue dissolved in 3N HCl (250mL). The solution was heated at 60°C for 6h. After this time the mixture was cooled to room temperature and extracted with DCM (6x). The combined organic layers were dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel, eluting with isohexane: EtOAc (4:1 $\rightarrow$ 1:1). The fractions containing the desired product were combined, evaporated and the residue triturated with ether. The title compound (1.8g, 5%) was isolated as a cream solid. mp 177 - 178°C. ^1H NMR (360MHz, d_6 – DMSO) δ 1.02 (6H,s), 2.19 (2H,s), 2.63 (2H,s), 6.23 (1H,t, J = 3.9Hz), 6.71 (1H,t, J = 3.9Hz). MS (ES^+) 164 (M+1).

Step 2: 6,6-Dimethyl-2-thiocyanato-4,5,6,7-tetrahydro-1H-indol-4-one

Potassium thiocyanate (1.2g, 12.3mmol) was dissolved in MeOH (4mL) and cooled to -70°C. The mixture was treated with bromine (0.31mL, 6.1mmol), maintaining the temperature below -60°C. After addition the mixture was warmed to -30°C and a solution of the indolone (1g, 6.1mmol) in MeOH (25mL) was added dropwise. The mixture was stirred for 30 min at -30°C then allowed to warm to room temperature and stirred for 3h. The mixture was poured onto ice water (30mL), the MeOH evaporated and the aqueous phase extracted with DCM (2x). The

combined organic layers were washed with water, $NaHCO_3$ (sat.) then separated and dried (Na_2SO_4). The solvent was evaporated and the residue triturated with ether. The title compound (0.83g, 62%) was isolated as a beige solid. ^1H NMR (360MHz, d_6 – DMSO) δ 1.03 (6H,s) 2.25 (2H,s), 2.68 (2H,s), 6.83 (1H,d, J = 1.9Hz), 12.44 (1H,br s). MS (ES^+) 221 (M+1).

Step 3: 6,6-Dimethyl-2-methylthio-4,5,6,7-tetrahydro-1H-indol-4-one

To a stirred solution of 6,6-dimethyl-2-thiocyanato-4,5,6,7-tetrahydro-1H-indol-4-one (400mg, 1.8mmol) and MeI (124μL, 2.0mmol) in MeOH (10mL) at -5°C was added a solution of KOH (117mg, 2.1mmol) in 1:1 MeOH/water (6mL), maintaining the temperature below 0°C. The mixture was stirred for 3h at room temperature, after which time the MeOH was removed and the residue partitioned between DCM and water. The organic layer was separated and the aqueous phase re-extracted with DCM. The combined organic layers were dried (Na_2SO_4) and evaporated to afford the title compound (350mg, 88%) as a colourless solid. mp 195 - 196°C. Found: C, 62.20; H, 7.13; N, 6.34%. Calc. $C_{11}H_{15}NOS.0.2(H_2O)$: C, 62.06; H, 7.29; N, 6.58%. ^1H NMR (360MHz, d_6 – DMSO) δ 1.02 (6H,s), 2.19 (2H,s), 2.34 (3H,s), 2.61 (2H,s), 6.30 (1H,d, J = 2.4Hz), 11.59 (1H,br s). MS (ES^+) 210 (M+1).

Step 4: 6,6-Dimethyl-3-methylthio-4,5,6,7-tetrahydro-1H-indol-4-one

6,6-Dimethyl-2-methylthio-4,5,6,7-tetrahydro-1H-indol-4-one (350mg, 1.7mmol) was heated at reflux in trifluoroacetic acid (4mL) and 1,2-dichloroethane (4mL) for 5h. After this time the mixture was evaporated and the residue partitioned between water (10mL) and DCM (10mL). The organic layer was separated and the aqueous phase extracted with DCM (2x). The combined organic layers were dried

(Na_2SO_4) and evaporated. The residue was chromatographed on silica gel, eluting with hexane: EtOAc (4:1), to afford the title compound (60mg, 17%) as a pink solid. ^{1}H NMR (360MHz, d_6 – DMSO) δ 1.01 (6H,s), 2.18 (2H,s), 2.27 (3H,s), 2.61 (2H,s), 6.53 (1H,d, J = 2.2Hz), 11.31 (1H,br s). MS (ES$^+$) 210 (M+1).

Step 5: 6,6-Dimethyl-3-methylthio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 1 using 6,6-dimethyl-3-methylthio-4,5,6,7-tetrahydro-1H-indol-4-one, the title compound (20mg, 30%) was isolated as a colourless solid. ^{1}HNMR (360MHz, d_6 – DMSO) δ 0.97 (6H,s) 2.24 (2H,s) 2.30 (3H,s), 2.92 (2H,s), 7.03 (1H,s), 7.37 (1H,dd, J = 7.1 and 5.0Hz), 7.60 (1H,d, J = 8.1Hz), 7.95 (1H,d of t, J = 7.7 and 1.9Hz), 8.50 – 8.53 (1H,m). MS (ES$^+$) 287 (M+1).

Example 13

6,6-Dimethyl-3-ethylthio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

Step 1: 6,6-Dimethyl-2-ethylthio-4,5,6,7-tetrahydro-1H-indol-4-one

In the same way as described for Example 12, Step 3 using ethyl iodide, the title compound (385mg, 48%) was isolated as a colourless solid. ^{1}H NMR (360MHz, d_6 – DMSO) δ 1.02 (6H,s), 1.13 (3H,t, J = 7.2Hz), 2.20 (2H,s), 2.62 (2H,s), 2.68 (2H,q, J = 7.2Hz), 6.36 (1H,d, J = 2.3Hz), 11.56 (1H,br s). MS (ES$^+$) 224 (M+1).

Step 2: 6,6-Dimethyl-3-ethylthio-4,5,6,7-tetrahydro-1H-indol-4-one

In the same way as described in Example 12, Step 4 using 6,6-dimethyl-2-ethylthio-4,5,6,7-tetrahydro-1H-indol-4-one, the title compound (100mg, 26%) was isolated as a colourless solid. ^{1}H NMR (360MHz, d_6 – DMSO) δ 1.01 (6H,s), 1.14 (3H,t, J = 7.4Hz), 2.19 (2H,s), 2.62 (2H,s), 2.75 (2H,q, J = 7.2Hz), 6.64 (1H,d, J = 2.3Hz), 11.33 (1H,br s). MS (ES$^+$) 224 (M+1).

Step 3: 6,6-Dimethyl-3-ethylthio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 1 using 6,6-dimethyl-3-ethylthio-4,5,6,7-tetrahydro-1H-indol-4-one, the title compound (80mg, 60%) was isolated as a cream solid. mp 158 - 159°C. Found: C, 67.49; H, 6.60; N, 9.08%. Calc. $C_{17}H_{20}N_2OS.0.1(H_2O)$: C, 67.56; H, 6.74; N, 9.27%. ^{1}H NMR (360MHz, d_6 – DMSO) δ 1.02 (6H,s), 1.25 (3H,t, J = 7.3Hz), 2.30 (2H,s), 2.86 (2H,q, J = 7.3Hz), 2.97 (2H,s), 7.18 (1H,s), 7.43 (1H,dd, J = 7.5 and 4.9Hz), 7.65 (1H,d, J = 8.1Hz), 8.02 (1H,d of t, J = 7.9 and 1.9Hz), 8.57 – 8.62 (1H,m). MS (ES$^+$) 301 (M+1).

Example 14

6,6-Dimethyl-3(phenylmethyl)thio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

Step 1: 6,6-Dimethyl-2-(phenylmethyl)thio-4,5,6,7-tetrahydro-1H-indol-4-one

In the same way as described for Example 12, Step 3 using benzyl bromide, the title compound (457mg, 72%) was obtained as a cream

solid. mp 148-150°C. Found: C, 70.90; H, 6.46; N, 5.02%. Calc. $C_{17}H_{19}NOS.0.15(H_2O)$: C, 70.87; H, 6.75; N, 4.86%. ^1H NMR (360MHz, $CDCl_3$) δ 1.07 (6H,s), 2.31 (2H,s), 2.47 (2H,s), 3.82 (2H,s), 6.67 (1H,d, J = 2.4Hz), 7.08 – 7.12 (2H,m), 7.23 – 7.26 (3H,m), 7.56 (1H,br s). MS (ES^+) 286 (M+1).

<u>Step 2: 6,6-Dimethyl-3-(phenylmethyl)thio-4,5,6,7-tetrahydro-1H-indol-4-one</u>

In the same way as described in Example 12, Step 4 using 6,6-dimethyl-2(phenylmethyl)thio-4,5,6,7-tetrahydro-1H-indol-4-one, the title compound (64mg, 15%) was isolated as a cream solid. mp 220 - 223°C. Found: C, 68.43; H, 6.31; N, 4.66%. Calc. $C_{17}H_{19}NOS.0.65(H_2O)$: C, 68.72; H, 6.89; N, 4.71%. ^1H NMR (360MHz, $CDCl_3$ + d_4–MeOH) δ 1.00 (6H,s), 2.24 (2H,s), 2.53 (2H,s), 3.92 (2H,s), 6.34 (1H,s), 7.04 – 7.11 (5H,m). MS (ES^+) 286 (M+1).

<u>Step 3: 6,6-Dimethyl-3(phenylmethyl)thio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one</u>

In the same way as described in Example 1 using 6,6-dimethyl-3-(phenylmethyl)thio-4,5,6,7-tetrahydro-1H-indol-4-one, the title compound (17mg, 27%) was obtained as a cream solid. mp 190 - 192°C. Found: C, 70.66; H, 5.84; N, 7.50%. Calc. $C_{22}H_{22}N_2OS.0.1(CH_2Cl_2).0.2(H_2O)$: C, 70.86; H, 6.08; N, 7.48%. ^1H NMR (360MHz, $CDCl_3$) δ 1.11 (6H,s), 2.43 (2H,s), 2.94 (2H,s), 4.14 (2H,s), 6.89 (1H,s), 7.19 – 7.34 (7H,m), 7.79 – 7.84 (1H,m), 8.52 – 8.56 (1H,m). MS (ES^+) 363 (M+1).

Example 15

6,6-Dimethyl-1-(pyridin-2-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

Step 1: 6,6-Dimethyl-1-(triisopropylsilyl)-4,5,6,7-tetrahydroindol-4-one

A solution of 6,6-dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one (3.8g, 23mmol) in DMF (25mL) was cooled to 0°C and NaH (1.02g of a 60% dispersion in mineral oil, 26mmol) was added portionwise. The mixture was stirred for 30 min then triisopropylsilyl chloride (5.6mL, 26mmol) was added at 0°C and stirring continued for 1 hr. The mixture was warmed to room temperature then extracted with ether (3x). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel, eluting with isohexane: EtOAc (9:1), to give the title compound (2.9g, 39%) as a colourless solid. ^1H NMR (360MHz, $CDCl_3$) δ 1.11 (6H,s), 1.14 (18H,d, J = 7.5Hz) 1.51 (3H,heptet, J = 7.5Hz), 2.34 (2H,s), 2.71 (2H,s), 6.64 (1H,d, J = 3.1Hz), 6.71 (1H,d, J = 3.1Hz). MS (ES^+) 320 (M+1).

Step 2: 3-Bromo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one

A solution of 6,6-dimethyl-1-(triisopropylsilyl)-4,5,6,7-tetrahydroindol-4-one (410mg, 1.28mmol) in THF (20mL) was cooled to -70°C and N-bromosuccinimide (228mg, 1.28mmol) was added. Stirring was continued at -70°C for 1h then warmed to room temperature. After attaining room temperature, tetrabutylammonium fluoride (1.28mL of a 1.0M solution in THF, 1.28mmol) was added and stirring continued for 5 min. Ether (20mL) was added, followed by water, and the organic layer separated. The aqueous phase was extracted with ether and the combined organic layers were dried ($MgSO_4$) and evaporated. The

residue was purified on silica gel, eluting with DCM, to give the title compound (210mg, 68%) as a colourless solid. ^{1}H NMR (360MHz, d_6 – DMSO) δ 1.02 (6H,s), 2.22 (2H,s), 2.64 (2H,s), 6.89 (1H,d, J = 2.4Hz), 11.58 (1H,br s). MS (ES$^+$) 242/244 (M+1).

Step 3: 3-Bromo-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 1 using 3-bromo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one, the title compound (600mg, 61%) was isolated as a pale yellow solid. mp 168 - 170°C. Found: C, 56.00; H, 4.64; N, 8.75%. Calc. $C_{15}H_{15}BrN_2O$. 0.1 (H_2O): C, 56.13; H, 4.77; N, 8.73%. ^{1}HNMR (360MHz, d_6 – DMSO) δ 1.03 (6H,s), 2.33 (2H,s), 2.98 (2H,s), 7.47 (1H,dd, J= 7.5 and 5.5Hz). 7.55 (1H,s). 7.66 (1H,d, J = 8.3Hz), 8.04 (1H,d or t, J = 7.7 and 1.9Hz), 8.57 – 8.62 (1H,m), MS (ES$^+$) 319/321 (M+1).

Step 4: 6,6-Dimethyl-1-(pyridin-2-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

A solution of 3-bromo-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one (100mg, 0.31mmol) and 2-(n-tributylstannyl) thiazole (175mg, 0.47mmol) in dioxan (10mL) was degassed with nitrogen from 30 min. Tetrakis (triphenylphosphine) palladium (75mg, 0.06mmol) was added and the mixture heated at reflux for 24h. The solvent was evaporated and the residue purified on silica gel, eluting with isohexane: EtOAc (9:1 → 1:1). The fractions containing the desired product were combined and evaporated. The resultant orange solid was triturated with isohexane and the title compound (75mg, 74%) isolated as a cream solid. mp 166 - 168°C. Found: C, 66.26; H, 5.27; N, 12.66%. Calc. $C_{18}H_{17}N_3OS.0.2(H_2O)$: C, 66.11; H, 5.36; N, 12.85%. ^{1}H NMR

(360MHz, $CDCl_3$) δ 1.15 (6H,s), 2.50 (2H,s), 3.04 (2H,s), 7.31 – 7.35 (2H,m), 7.45 (1H,d, J = 6.3Hz), 7.78 (1H,d, J = 3.2Hz), 7.86 (1H,d of t, J = 7.8 and 1.9Hz), 7.91 (1H,s), 8.56 – 8.60 (1H,m). MS (ES^+) 324 (M+1).

Example 16

6,6-Dimethyl-3-phenyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

A solution of 3-bromo-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one (100mg, 0.31mmol), phenylboronic acid (153mg, 1.25mmol), tetrakis(triphenylphosphine)palladium (50mg, 0.04mmol) and Na_2CO_3 (197mg, 1.9mmol) in ethylene glycol dimethyl ether (10mL) and water (4mL) was heated at reflux for 8h. The solvent was evaporated and the residue partitioned between DCM and aqueous K_2CO_3 (10% ($^W/_V$)). The organic layer was separated and the aqueous phase re-extracted with DCM (2x). The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel, eluting with isohexane: EtOAc (9:1), to afford the title compound (60mg, 61%) as a yellow solid. mp 160-162°C. Found: C, 78.23; H, 6.26; N, 8.57%. Calc. $C_{21}H_{20}N_2O.0.35(H_2O)$: C, 78.16; H, 6.47; N, 8.68%. ^1H NMR (360MHz, $CDCl_3$) δ 1.13 (6H,s), 2.45 (2H,s), 2.99 (2H,s), 7.17 (1H,s), 7.24 – 7.38 (5H,m), 7.67 (2H,d, J = 7.2Hz), 7.86 (1H,d of t, J = 7.9 and 1.9Hz), 8.56 – 8.61 (1H,m). MS (ES^+) 317 (M+1).

Example 17

6,6-Dimethyl-1-(pyridin-2-yl)-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 15, Step 4 using 2-(tributylstannyl)pyridine, the title compound (40mg, 40%) was isolated as a cream solid. mp 171-174°C. Found: C, 74.55; H, 5.89; N, 12.61%. Calc. $C_{20}H_{19}N_3O.0.35(H_2O)$: C, 74.21; H, 6.13; N, 12.98%. ^{1}HNMR (360MHz, $CDCl_3$) δ 1.14 (6H,s), 2.49 (2H,s), 3.03 (2H,s), 7.15 (1H,dd, J = 6.3 and 3.8Hz), 7.31 (1H,dd, J = 7.5 and 4.9Hz), 7.48 (1H,d, J = 8.2Hz), 7.70 – 7.73 (2H,m), 7.86 (1H,d of t, J = 7.8 and 1.9Hz), 8.32 (1H,d, J = 8.1Hz), 8.55 – 8.59 (2H,m). MS (ES^+). 318 (M+1).

Example 18

6,6-Dimethyl-1-(pyridin-2-yl)-3-vinyl-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 15, Step 4 using tributyl(vinyl)tin, the title compound (45mg, 54%) was isolated as a cream solid. mp 150 - 154°C. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.11 (6H,s), 2.40 (2H,s), 2.93 (2H,s), 5.18 (1H,dd, J = 11 and 1.8Hz), 5.72 (1H,dd, J = 18 and 1.8Hz), 7.22 (1H,dd, J = 18 and 11Hz), 7.26 – 7.35 (3H,m), 7.85 (1H,d of t, J = 7.7 and 1.9Hz), 8.55 – 8.58 (1H,m). MS (ES^+) 267 (M+1).

Example 19

6,6-Dimethyl-3-phenylmethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

A solution of 3-bromo-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one (100mg, 0.31mmol), benzyltributylstannane (253mg, 0.68mmol) and dichlorobis(triphenylphosphine)palladium (50mg, 0.08mmol) in hexamethylphosphoramide (1mL) was heated at 70°C for 48h. The mixture was cooled to room temperature, diluted with DCM (2mL), and the solution chromatographed on silica gel, eluting with isohexane: EtOAc (4:1). The title compound (45mg, 43%) was isolated as a colourless solid. mp 111 - 113°C. Found: C, 79.7; H, 6.7; N, 8.3%. Calc. $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48%. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.11 (6H,s), 2.39 (2H,s), 2.93 (2H,s), 4.17 (2H,s), 6.61 (1H,s), 7.16 – 7.34 (7H,m), 7.77 (1H, d of t, J = 7.7 and 1.9Hz), 8.50 – 8.53 (1H,m). MS (ES^+) 331 (M+1).

Example 20

6,6-Dimethyl-3-(oxazol-2-yl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 15, Step 4 using 2-tributylstannyloxazole, the title compound (50mg, 52%) was afforded as a cream solid. mp 194 - 196°C. Found: C, 70.30; H, 5.25; N, 13.48%. Calc. $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67%. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.13 (6H,s), 2.50 (2H,s), 3.00 (2H,s), 7.20 (1H,s), 7.36 (1H,dd, J = 6.7 and 4.3Hz), 7.41 (1H,d, J = 7.4Hz), 7.73 (1H,s), 7.75 (1H,s), 7.89 (1H,d of t, J = 6.9 and 1.7Hz), 8.57 – 8.60 (1H,m). MS (ES^+) 308 (M+1).

Example 21

6,6-Dimethyl-1-(pyridin-2-yl)-3-(thiazol-5-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 15, Step 4 using 5-tributylstannylthiazole, the title compound (73mg, 72%) was obtained as a yellow solid. mp 167 - 169°C. Found: C, 64.96; H, 5.23; N, 12.01%. Calc. $C_{18}H_{17}N_3OS.0.1(Et_2O).0.45\ (H_2O)$: C, 65.20; H, 5.62; N, 12.40%. ^1H NMR (400MHz, $CDCl_3$) δ 1.14 (6H,s), 2.47 (2H,s), 2.97 (2H,s), 7.33 – 7.39 (3H,m), 7.90 (1H,d of t, J = 7.7 and 1.9Hz), 8.41 (1H,s), 8.57 – 8.60 (1H,m), 8.70 (1H,s). MS (ES^+) 324 (M+1).

Example 22

6,6-Dimethyl-3-phenylamino-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

A suspension of 3-bromo-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one (50mg, 0.16mmol), aniline (17μL, 0.19mmol), sodium *tert*-butoxide (18mg, 0.19mmol) tris(dibenzylideneacetone)dipalladium (7.2mg, 0.008mmol) and (R)-(+)-2,2′-bis(diphenylphosphino)-1,1-binaphthyl (9.8mg, 0.016mmol) in toluene (3mL) was heated at reflux for 3h. The toluene was evaporated and the residue chromatographed on silica gel, eluting with isohexane: EtOAc (9:1 → 4:1). The title compound (23mg, 43%) was isolated as a yellow solid. mp 135 - 138°C. Found: C, 73.98; H, 6.10; N, 12.33%. $C_{21}H_{21}N_3O.0.45(H_2O)$: C,74.29; H, 6.50; N, 12.38%. ^1H NMR (360MHz, d_6-DMSO) δ 1.07 (6H,s), 2.37 (2H,s), 3.03 (2H,s), 6.81 (1H,t, J = 7.4Hz), 7.08 (2H,d, J = 7.7Hz), 7.25 – 7.29 (2H,m), 7.41 (1H,dd, J = 7.2 and

and 4.9Hz), 7.72 (1H,d, J = 8.1Hz), 8.01 (1H,d of t, J = 7.6 and 1.8Hz), 8.16 (1H,s), 8.57 – 8.60 (1H,m). MS (ES^+) 332 (M+1).

Example 23

6,6-Dimethyl-1-(pyridin-2-yl)-3-(pyridin-2-ylamino)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 22 using 2-aminopyridine, the title compound (20mg, 23%) was isolated as a yellow solid. mp 180 - 183°C. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.13 (6H,s), 2.41 (2H,s), 3.04 (2H,s), 6.65 – 6.69 (1H,m), 6.73 (1H,d, J = 8.5Hz), 7.24 (1H,dd, J = 7.4 and 4.9Hz), 7.44 – 7.48 (2H,m), 7.83 (1H,d of t, J = 7.9 and 1.9Hz) 7.91 (1H,s), 8.26 – 8.30 (1H,m), 8.53 – 8.57 (1H,m), 8.74 (1H,s). MS (ES^+) 333 (M+1).

Example 24

6,6-Dimethyl-3-ethyl-1-(6-methylpyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 1 using 2-fluoro-6-methylpyridine, the title compound (15mg, 17%) was isolated as a cream solid. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.09 (6H,s), 1.23 (3H,t, J = 7.4Hz) 2.37 (2H,s), 2.58 (3H,s), 2.81 (2H,q, J = 7.4Hz), 2.89 (2H,s), 6.89 (1H,s), 7.07 – 7.12 (2H,m), 7.69 (1H,t, J = 7.8Hz). MS (ES^+) 283 (M+1).

Example 25

6,6-Dimethyl-3-(4-methylthiazol-5-yl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 15, Step 4 using 2-(tributylstannyl)-4-methylthiazole the title compound (52mg, 19mg) was isolated. ^{1}H NMR (400MHz, d_6-DMSO) δ 1.06 (6H,s), 2.37 (3H,s), 2.43 (2H,s), 3.01 (2H,s) 7.16 (1H,s), 7.50 (1H,dd, J = 7.3 and 4.9Hz), 7.77 (1H,d, J = 8.2Hz), 7.94 (1H,s), 8.06 (1H,d of t, J = 8.0 and 1.7Hz), 8.61 – 8.63 (1H,m). MS (ES^+) 338 (M+1).

Example 26

3-(4-Chlorophenyl)-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

A solution of 3-bromo-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one (50mg, 0.16mmol) and tetrakis(triphenylphosphine)palladium (15mg, 0.01mmol) in ethylene glycol dimethyl ether (2mL) at 45°C was degassed with nitrogen for 30 min. A degassed solution of Cs_2CO_3 (104mg, 0.16mmol) in water (1mL) was added followed by 4-chlorophenylboronic acid (25mg, 0.16mmol). The solution was heated at 100°C for 18h then filtered through celite. The filtrate was partitioned between DCM and water. The organic phase was separated, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting with isohexane: EtOAc (3:1) to give the title compound (6mg, 11%) as a colourless solid. ^{1}H NMR (360MHz, d_6-DMSO) δ 1.05 (6H,s), 2.37 (2H,s), 3.01 (2H,s), 7.38 (2H,d, J = 8.5Hz), 7.46 – 7.50 (1H,m), 7.56 (1H,s), 7.68 – 7.74 (3H,m), 8.05 – 8.09 (1H,m), 8.59 – 8.63 (1H,m). MS (ES^+) 351/353 (M+1).

Example 27

3-(3-Chlorophenyl)-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 26 using 3-chlorophenylboronic acid, the title compound (71mg, 43%) was isolated as a colourless solid. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.13 (6H,s), 2.46 (2H,s), 2.98 (2H,s), 7.20 (1H,s), 7.23 – 7.39 (4H,m), 7.60 (1H,t of d, J = 7.3 and 1.5Hz), 7.66 (1H,t, J = 1.8Hz), 7.88 (1H,d of t, J = 7.9 and 1.9Hz), 8.57 – 8.60 (1H,m). MS (ES^+) 351/353 (M+1).

Example 28

3-(2-Chlorophenyl)-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 26 using 2-chlorophenylboronic acid, the title compound (44mg, 27%) was isolated as a colourless solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.14 (6H,s), 2.40 (2H,s), 3.02 (2H,s), 7.16 (1H,s), 7.23 – 7.26 (2H,m), 7.30 (1H,dd, J = 7.4 and 5.0Hz), 7.38 (1H,d, J = 8.1Hz), 7.41 – 7.44 (2H,m), 7.87 (1H,d of t, J = 7.6 and 1.9Hz), 8.56 – 8.58 (1H,m). MS (ES^+) 351/353 (M+1).

Example 29

6,6-Dimethyl-1-(pyridin-3-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

Step1: 3-Bromo-6,6-dimethyl-1-(pyridin-3-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 4 using 3-bromopyridine, the title compound (72mg, 8%) was isolated as a brown solid. ^{1}H NMR (360MHz, d_6-DMSO) δ 1.00 (6H,s) 2.31 (2H,s), 2.71 (2H,s), 7.40 (1H,s), 7.60 (1H,dd, J = 8.4 and 4.8Hz), 7.95 – 7.99 (1H,m), 8.67 – 8.70 (1H,m), 8.73 – 8.76 (1H,m). MS (ES$^+$) 319/321 (M+1)

Step 2: 6,6-Dimethyl-1-(pyridin-3-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 15, Step 4 using 6,6-dimethyl-1-(pyridin-3-yl)-3-(thiazol-2-yl-4,5,6,7-tetrahydroindol-4-one and 2-tributylstannylthiazole, the title compound (12mg, 10%) was isolated as a colourless solid. ^{1}H NMR (400MHz, d_6-DMSO) δ 1.05 (6H,s), 2.42 (2H,s), 2.75 (2H,s) 7.61 – 7.65 (2H,m), 7.78 – 7.81 (2H,m), 8.05 – 8.08 (1H,m), 8.70 – 8.71 (1H,m). MS (ES$^+$) 324 (M+1).

Example 30

1-(5-Chloropyridin-2-yl)-6,6-dimethyl-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

Step 1: 3-Bromo-1-(5-chloropyridin-2-yl)-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 1 using 3-bromo-6,6-dimethyl-1,2,3,4-tetrahydro-1H-indol-4-one and 2,5-dichloropyridine, the title compound (212mg, 36%) was isolated as a yellow solid.

Step 2: 1-(5-Chloropyridin-2-yl)-6,6-dimethyl-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 15, Step 4 using 3-bromo-1-(5-chloropyridin-2-yl)-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one and 2-tributylstannylthiazole, the title compound (73mg, 37%) was isolated as a pale yellow solid. ^{1}H NMR (400MHz, d_6-DMSO) δ 1.06 (6H,s), 2.44 (2H,s), 3.01 (2H,s), 7.63 (1H,d, J = 3Hz), 7.80 – 7.84 (2H,m), 8.00 (1H,s), 8.20 (1H,dd, J = 8.6 and 2.6Hz), 8.69 (1H,d, J = 2.6Hz). MS (ES$^+$) 358/360 (M+1).

^{1}H NMR (400MHz, d_6-DMSO) δ 1.02 (6H,s), 2.33 (2H,s), 2.97 (2H,s), 7.56 (1H,s), 7.71 (1H,d, J = 8.6Hz), 8.18 (1H,dd, J = 8.7Hz and 2.6Hz), 8.64 (1H,d, J = 2.6Hz). MS (ES$^+$) 353/355 (M+1).

Example 31

6,6-Dimethyl-3-(thiazol-2-yl)-1-(6-(thiazol-2-yl)pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

Step 1: 3-Bromo-1-(6-chloropyridin-2-yl)-6,6-dimethyl-1,2,3,4-tetrahydroindol-4-one

In the same way as described in Example 1 using 3-bromo-6,6-dimethyl-1,2,3,4-tetrahydro-1H-indol-4-one and 2,6-dichloropyridine, the title compound (232mg, 40%) was isolated as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.14 (6H,s), 2.42 (2H,s), 2.96 (2H,s), 7.17 (1H,s), 7.22 (1H,d, J = 8.0Hz), 7.33 (1H,d, J = 7.9Hz), 7.82 (1H,t, J = 7.8Hz). MS (ES^+) 353/355 (M+1).

Step 2: 6,6-Dimethyl-3-(thiazol-2-yl)-1-(6-(thiazol-2-yl)pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 15, Step 4 using 3-bromo-1-(6-chloropyridin-2-yl)-6,6-dimethyl-1,2,3,4-tetrahydroindol-4-one and 2-tributylstannylthiazole, the title compound (35mg; 13%) was isolated as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.21 (6H,s), 2.55 (2H,s), 3.24 (2H,s) 7.35 (1H,d, J = 3.1Hz), 7.50 – 7.53 (2H,m), 7.81 (1H,d, J = 3.1Hz), 7.97 – 8.02 (3H,m), 8.20 (1H,d, J = 7.8Hz). MS (ES^+) 407 (M+1).

Example 32

1-(2-Cyanophenyl)-6,6-dimethyl-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

Step 1: 3-Bromo-1-(2-cyanophenyl)-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one

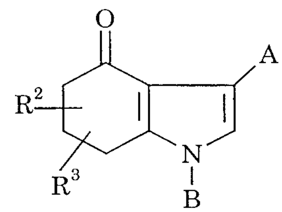
A solution of 3-bromo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one (670mg, 2.77mmol), 2-fluorobenzonitrile (0.3mL, 2.77mmol) and K_2CO_3 (957mg, 6.9mmol) in DMSO (10mL) was stirred at 100°C for 3h. The mixture was cooled to room temperature, poured into water and extracted into EtOAc (3x). The combined organic layers were washed with water (2x), dried ($MgSO_4$) and evaporated. The title compound (858mg, 91%) was isolated as a beige solid and used without further purification. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.10 (6H,s), 2.42 (2H,s), 2.51 (2H,s), 6.83 (1H,s), 7.42 (1H,dd, J = 7.9 and 0.9Hz), 7.64 (1H,dd, J = 7.7 and 1.1Hz), 7.78 (1H,dd, J = 7.9 and 1.5Hz), 7.85 (1H,dd, J = 7.7 and 1.4Hz). MS (ES$^+$) 343/345 (M+1).

Step 2: 1-(2-Cyanophenyl)-6,6-dimethyl-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 15, Step 4 using 3-bromo-1-(2-cyanophenyl)-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one and 2-tributylstannylthiazole, the title compound (200mg, 44%) was isolated as a colourless solid. ^{1}H NMR (400MHz, d_6-DMSO) δ 1.05 (6H,s), 2.43 (2H,s), 2.53 (2H,s), 7.63 (1H,d, J = 3.3Hz), 7.75 – 7.80 (4H,m), 7.92 (1H,dd, J = 7.8 and 1.4Hz), 8.13 (1H,dd, J = 7.7 and 1.3Hz). MS (ES$^+$) 348 (M+1).

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

where A is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, arylC_{1-6}alkyl, or aryl wherein the aryl group is optionally substituted by halogen, C_{1-6} alkyl, CF_3, CN, NO_2 or NH_2, NR^1R^{10}, $S(O)_pR^1$, heteroarylC_{1-6}alkyl or heteroaryl where heteroaryl is a 5- or 6-membered heteroaromatic ring as defined for B below;

B is phenyl or a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, a 6-membered heteroaromatic ring containing 1, 2, 3 or 4 nitrogen atoms, each of which rings is optionally substituted by one or more substituents independently chosen from: cyano; C_{1-6}alkyl; C_{1-6}haloalkyl; halogen; $S(O)_rR^4$; COR^5; and aryl, arylC_{1-6}alkyl or a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N wherein the aryl ring or 5-membered ring is optionally substituted by one, two or three substituents independently chosen from halogen, CF_3, OCH_3, nitro and cyano; and when a nitrogen ring atom is present it is optionally substituted by oxygen;

R^1 is hydrogen; C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl or C_{3-6}cycloalkenyl each of which is optionally substituted by amino,

C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, C_{1-6}alkoxy, C_{1-6}alkylaminocarbonyl, one, two or three hydroxy groups, one, two or three halogen atoms or a four, five or six-membered saturated heterocyclic ring containing a nitrogen atom and optionally either an oxygen atom or a further nitrogen atom which ring is optionally substituted by C_{1-4}alkyl on the further nitrogen atom; aryl, arylC_{1-6}alkyl, arylC_{2-6}alkenyl or arylC_{2-6}alkynyl optionally substituted on the aryl ring by halogen, nitro, cyano, C_{1-6}alkylcarbonylamino, hydroxy or C_{1-6}alkoxy; or a five-membered aromatic ring containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, or a six-membered aromatic ring containing 1, 2, 3 or 4 nitrogen atoms, which ring is optionally substituted by halogen, C_{1-6}alkoxy, C_{1-6}alkylthio, aryl, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

R^2 and R^3 are independently hydrogen or C_{1-6}alkyl or together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group;

R^4 is hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl or $CH_2(CO)_mNR^8R^9$;

R^5 is NR^6R^7, C_{1-6}alkyl or C_{1-6}alkoxy;

R^6 is independently as defined for R^4;

R^7 is aryl optionally substituted by halogen, nitro or cyano;

R^8 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{2-6}alkenyl, C_{2-6}alkynyl; arylC_{1-6}alkyl, arylC_{2-6}alkenyl or arylC_{2-6}alkynyl optionally substituted on the aryl ring by halogen, nitro or cyano; thiophene or pyridine;

R^9 is C_{1-6}alkyl; C_{2-6}alkenyl; C_{2-6}alkynyl; or phenyl optionally substituted by one, two or three substituents independently chosen from halogen, CF_3, OCH_3, nitro and cyano;

R^{10} is hydrogen or C_{1-6} alkyl;

R^{14} is hydrogen or C_{1-6}alkyl;

m is zero or 1;

p is zero, 1 or 2;

q is 1 or 2;
r is 0, 1 or 2;
s is 0, 1 or 2; and
t is 0, 1 or 2.

2. A compound according to claim 1 wherein B is an optionally substituted phenyl or optionally substituted 6-membered heteroaromatic ring. The optional substituents are preferably one or two groups independently chosen from halogen, C_{1-6}alkyl, trifluoromethyl, cyano and an unsubstituted 5-membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S in which not more than one heteroatom is other than N.

3. A compound according to claim 1 or 2 wherein A is C_{1-6}alkyl, C_{2-6}alkenyl, arylC_{1-6}alkyl or aryl wherein the aryl group is optionally substituted by a halogen atom or a C_{1-6}alkyl group, a 5- or 6-membered heteroaromatic ring optionally substituted by a halogen atom or C_{1-6}alkyl, NHR^1 or SR^1.

4. A compound according to claim 1, 2 or 3 wherein R^1 is C_{1-6}alkyl, C_{1-4}alkenyl, or C_{3-6}cycloalkyl each of which is optionally substituted by di(C_{1-4}alkyl)amino, C_{1-4}alkoxy, C_{1-4}alkylaminocarbonyl, one or two hydroxy groups or three fluorine atoms; phenyl or phenylC_{1-4}alkyl optionally substituted on the phenyl ring by chlorine, fluorine, C_{1-4}alkoxy or C_{1-4}alkylcarbonylamino; or a pyridine, thiophene, furan, pyrimidine, thiazole, imidazole, triazole or thiadiazole, each of which is unsubstituted or substituted by C_{1-4}alkyl, phenyl, fluorine or C_{1-4}alkylthio.

5. A compound according to anyone of claims 1 to 4 wherein R^2 and R^3 are independently chosen from hydrogen and methyl.

6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

7. A compound according to anyone of claims 1 to 5, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by surgery, therapy or diagnosis.

8. Use of a compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the treatment or prevention of a condition requiring the administration of a ligand selective for $GABA_A$ receptors containing the $\alpha5$ subunit.

9. A method of treatment or prevention of a condition associated with $GABA_A$ receptors containing the $\alpha5$ subunit in a subject suffering from or prone to such a condition which comprises administering to that subject a therapeutically or propylactically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/01799

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 A61K31/40 C07D403/04 C07D417/04 C07D209/08
C07D417/14 C07D401/14 C07D413/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 150 397 A (PARKE, DAVIS & COMPANY) 30 April 1969 (1969-04-30) page 9, line 17 - line 19 ---	1-3,5
X	BRIAN G. MCDONALD ET AL.: "Conversion of 2-Chloroallylamines into Heterocyclic Compounds. Part I. 2-Methylindoles, 1,5,6,7-Tetrahydro-3-methylindol-4-ones, and Related Heterocycles" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, vol. 15, - 1975 pages 1446-1450, XP002114574 LETCHWORTH GB * page 1449, right column: compounds of formula XVII with X = 3-Me and R = Ph or p-ClC6H4 * ---	1-3,5

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 September 1999	22/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/01799

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 18792 A (MERCK SHARP & DOHME LTD.) 7 May 1998 (1998-05-07) claims 1,8	1,6-8
A	WO 97 34870 A (NEUROGEN CORPORATION) 25 September 1997 (1997-09-25) page 11 - page 12	1,6,7

INTERNATIONAL SEARCH REPORT

Int .tional application No.

PCT/GB 99/01799

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 9
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

I. mation on patent family members

Internat' al Application No
PCT/GB 99/01799

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1150397 A	30-04-1969	NONE	
WO 9818792 A	07-05-1998	AU 4787797 A	22-05-1998
		EP 0937072 A	25-08-1999
WO 9734870 A	25-09-1997	AU 2218997 A	10-10-1997
		EP 0888300 A	07-01-1999